

In re Application of:  
Rheins and Morhenn  
Application No.: 09/375,609  
Filed: August, 17, 1999  
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PATENT  
Attorney Docket No.: DERM1100-1

### **REMARKS**

Claims 64-65, 71-72, 76-78, 80-83, 85-87, 149-161 and 163-164 are pending and under consideration. Claims 76, 77, 85-87, 149-156, 160, and 163, have been canceled herein without prejudice or disclaimer. Claims 64, 78, and 80-83, have been amended herein, as indicated in the Listing of Claims. Claim 165-175 have been added. After entry of the present Amendment, claims 64-65, 71-72, 78, 80-83, 157-159, 161, and 164-175 will be pending and under consideration.

The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendment to claim 64 and newly added claim 167 are supported by claims 1, 6, and 8 as filed. The amendments to claims 78, 80-83, and 164 change dependencies or otherwise render these claims consistent with the amendment to claim 64. Newly added claims 165, 166, and 168-175 are similar to previously entered amendments and are supported by the disclosure at page 18, first full paragraph, which indicates that multiple tape strips can be used at one skin site, page 19, first full paragraph, and the description of Figure 1 (page 4, line 20) which indicates that 12 tape strippings were used, and page 3, lines 14-15, which indicates that the adhesive tape can be applied one or more times. Applicants respectfully request entry of the amendments and reconsideration of the application in view of the comments herein.

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**Claim Rejection Under 35 U.S.C. §101**

Claim 160 stands rejected under 35 U.S.C. §101 as allegedly lacking patentable utility. Claim 160 is canceled herein. Therefore, the rejection is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 160 under 35 U.S.C. §101.

**Claim Rejection Under 35 U.S.C. §102(b)**

Claims 64, 65, 76, 85, 86, and 161 remain rejected under 35 U.S.C. §102(b) as anticipated and claim 70 as anticipated under 35 U.S.C. §102(b) and optionally under 35 U.S.C. §103, as obvious over Garofano et al. Applicants respectfully traverse the rejection. To anticipate an invention, each and every element of a claim must be found in a single prior art reference. MPEP § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Office Action cites *In re Best* 195 USPQ 430, 433 (CCPA 1977) in its rejection. In *In re Best* the court states that where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may in fact be an inherent characteristic of the prior art, the Patent Office has the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

In response to Applicants arguments in the Response mailed September 9, 2003, the Office Action alleges that the Applicants were merely speculating in their argument that Garofano et al. do not provide adequate controls to indicate to one of ordinary skill in the art that they successfully amplified DNA from a skin sample obtained from tape strips. Furthermore, the Office Action alleges that there are no limitations in the claims directed at success rate, and no showing of surprise results.

Claims 70, 76, 85, and 86 are canceled herein, without prejudice or disclaimer. Therefore, with respect to claim 70, 76, 85, and 86 the rejection is moot. With respect to claims 64, 65, and 161, which remain pending upon entry of the present amendments, claim 64, from which claims 65 and 161 depend, recites that RNA is isolated and that levels of RNA in the skin sample are compared to a

control sample, thereby quantitating relative expression of the RNA. Garofano et al. is silent with respect to isolating RNA and silent with respect to quantitating relative expression of any nucleic acid, including RNA. Furthermore, since Garofano et al. is silent with respect to quantitation of any nucleic acid and silent with respect to RNA isolation, there is no inherent teaching in Garofano et al. that RNA is isolated or quantitated. Therefore, Applicants respectfully assert that Garofano et al. does not disclose, either explicitly or inherently, isolation of RNA by applying an adhesive tape to skin, or quantitation of relative expression of an RNA by comparing the level of the RNA in the skin to a control sample. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 64, 65, 76, 85, 86, and 161 under 35 U.S.C. §102(b) as anticipated and claim 70 as anticipated under 35 U.S.C. §102(b) and optionally under 35 U.S.C. §103, as obvious over Garofano et al.

Claims 71-72 remain rejected under 35 U.S.C. § 103(a) over Garofano et al. *Adv. Forensic Haemogentet*, 6:281-83 (1996). Applicants respectfully traverse the rejection. To establish a *prima facie* case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP §2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Furthermore, in order to render a claimed apparatus or method obvious, the prior art must enable the invention. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (1989); and *Rockwell Int. Corp. v. United States*, 147 F3d 1358, 1364, 7 USPQ2D (BNA) 1027 (Fed. Cir. 1998). Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. MPEP § 2141; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

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The Office Action cites the allegations regarding Garofano et al. in the above rejection, and further alleges that with respect to claims that recite one or two tape strippings, it would have been obvious to a person of ordinary skill in the art to determine the minimum number of tape strippings. The Office Action alleges that the skilled artisan would have been motivated to use less tape strippings to minimize stress and trauma on the patient, and alleges that both are well-recognized motivations in the medical arts. Furthermore, in response to Applicants arguments that there is no motivation or reasonable expectation of success in Garofano et al. regarding applying an adhesive tape to the skin between one and two times, the Office Action cites Garofano's conclusion that the material stuck on adhesive tape can be considered an interesting source of DNA for investigation purpose. Furthermore, the Office Action cites Garofano et al.'s comments regarding performing genetic analysis using adhesive tapes that had been used to wrap packages during crimes and in kidnapping cases as evidence that Garofano et al. expected success even where only one tape stripping was used.

Claim 64, from which claims 71 and 72 depend, recites that RNA is isolated and that levels of RNA in a skin sample are compared to a control sample, thereby quantitating relative expression of the RNA. Garofano et al. is silent with respect to isolating RNA and silent with respect to quantitating relative expression of any nucleic acid, including RNA. Furthermore, since Garofano et al. is silent with respect to quantitation of any nucleic acid and silent with respect to RNA isolation, there is no inherent teaching in Garofano et al. that RNA is isolated and quantitated. Therefore, Applicants respectfully assert that Garofano et al. does not disclose, either explicitly or inherently, isolation of RNA by applying an adhesive tape to skin, or quantitation of relative expression of an RNA by comparing the level of the RNA in the skin to a control sample. Accordingly, Applicants respectfully assert that Garofano et al. do not teach or suggest all of the claimed limitations.

In addition to not teaching all of the claimed limitations, Garofano does not provide a motivation or reasonable expectation of success, nor does it enable, isolating RNA or quantitating any nucleic acids after applying an adhesive tape to skin to obtain a skin sample. Even for isolating

DNA, Garofano et al. report a relatively "low percentage of positive results" (page 282, last paragraph). As acknowledged in the Office Action, "*all* work involving RNA is difficult, because *all* tissues and cells are rich in RNAases" (Office Action page 3, first full paragraph). However, the Office Action alleges that "[t]here is no reason for the person of ordinary skill in the art to have expected skin cells obtained by tape stripping to be inordinately different in this respect."

Applicants respectfully assert that a skilled artisan would not expect cells of the outer layers of the skin (i.e. the stratum corneum) that are harvested by tape stripping to include intact RNA, especially not enough intact RNA to allow quantitation. Unlike almost all cells of the body, cells of the outer layers of the skin are devoid of organelles and do not actively transcribe RNA into protein.

Therefore, one of ordinary skill in the art would not expect success, or be motivated to isolate and quantitate RNA from skin samples by applying an adhesive tape to the skin by Garofano et al.'s disclosure of the isolation of DNA from some skin samples. Furthermore, isolation of DNA from some skin samples obtained by tape stripping does not enable the invention of the pending claims, which recites isolating RNA and quantitating relative expression of an RNA.

The fact that one of ordinary skill in the art would not have a reasonable expectation of success nor a motivation to use tape stripping to isolate and quantitate an RNA from the skin, is evidenced by the comments of NIH reviewers of a grant proposal that relies on methods of the present application, entitled "Non-Invasive Recovery of RNA from Human Epidermis", submitted by Dermtech International, the assignee of the present patent application, after the filing date of the present application (Exhibit A). For example, Reviewer 1 asserted that "Existence of intact cellular mRNA in the outermost layer of St. corneum is surprising" (Exhibit A, page 2, paragraph entitled "APPROACH"). Furthermore, Reviewer 2 asserted that "[t]here was some concern about the overall view of the investigators about skin biology and their hope that mRNA detection on the very superficial samples obtained from tape stripping would reflect salient mRNAs and DNA products that reflect what is going on [sic] in lower layers of the epidermis and the dermis" (Exhibit A, page 3, last paragraph.). Accordingly, Applicants assert that, as supported by Exhibit A, there is no

motivation or reasonable expectation of success for the claimed methods, based on the teachings of Garofano et al.

The patentability of the present invention over the cited art is further established by a number of secondary factors, including long-felt need, unexpected results, commercial success and skepticism of experts. For example, experts were skeptical and the results unexpected regarding the ability to isolate and quantitate RNA from the outermost layer of stratum corneum using tape stripping (See Exhibit A, Reviewer 1 comments on page 2, paragraph labeled "APPROACH," asserting that "Existence of intact cellular mRNA in the outermost layer of St. corneum is surprising"; and Reviewer 2 comments on page 3, last paragraph "[t]here was some concern about the over-all [sic] view of the investigators about skin biology and their hope that mRNA detection on the very superficial samples obtained from tape stripping would reflect salient mRNAs and DNA products that reflect what is going on [sic] in lower layers of the epidermis and the dermis"). Regarding long-felt need, it is recognized that there is an important need for a non-invasive method for performing RNA analysis of the stratum corneum (See Exhibit A, Reviewer 1 comment on page 2, paragraph labeled "CRITIQUE 1, "This is an excellent proposal to test an innovative idea that could fill an important commercial and scientific need"). Furthermore, it is acknowledged that RNA analysis of the skin using a non-invasive, rapid method is expected to find wide application and commercial success (Exhibit A, Reviewer 1 comments on page 2, paragraph labeled "SIGNIFICANCE"; Reviewer 2 comments on page 3, paragraph labeled "SIGNIFICANCE," "The idea of this grant proposal is novel and very advanced. This work would be the beginning of real molecular diagnoses in dermatology. It has the potential of making the overall entire field and discipline of dermatology revolutionized towards a more objective science for making the diagnoses and modulating therapy according to gene expression").

Further evidence regarding a lack of expectation of success and skepticism of experts regarding the invention of the pending claims is exemplified by publications that assert that it is not possible to reliably quantitate a molecule in the outermost layers of skin using tape stripping. Tape

harvesting or stripping of the stratum corneum has been used in dermatology for over 40 years to remove the outer layer of the epidermis to test for drug penetration pharmacokinetics. However, efforts to quantify the uptake of applied chemicals by assaying their content in the removed stratum corneum have encountered difficulty and skepticism (Bunge, A. and R. Guy (2003), "Improvement of methodology for assessing bioequivalence of topical products"

[http://www.fda.gov/ohrms/dockets/ac/03/slides/3996S2\\_07\\_Bunge.pdf](http://www.fda.gov/ohrms/dockets/ac/03/slides/3996S2_07_Bunge.pdf) (EXHIBIT B); and PRMA (1998), "Draft Guidance for Industry on Topical Dermatological Drug Product NDA's and ANDA's - In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies: Dermatopharmacokinetics (DPK) Method Issues:"

<http://srpub.phrma.org/letters/08.17.98.topical.derm.html> (EXHIBIT C)). This has lead to a withdrawal in 2003 of the FDA's guidance on using tape stripping for pharmacokinetic studies. This general opinion that tape stripping is not a sufficiently quantitative tool is powerfully evidenced by the opinion of the American Academy of Dermatology. In December of 1999 the Academy stated its opposition to the method (AAD, 1999) and suggested that that tape stripping was fundamentally doomed to failure (AAD (1999), Washington Report: Skin tape stripping method for generic dermatologic drug approval remains in question

[http://www.aadassociation.org/old/washReports/dec99\\_washrep.html](http://www.aadassociation.org/old/washReports/dec99_washrep.html) (EXHIBIT D)). Thus, it is evident that the practice of tape stripping was and is not viewed as a potentially quantitative method by two of the most influential associations in dermatological and pharmaceutical science. While these opinions are directed at the use of tape stripping for the dermatopharmacokinetic determination of bioequivalence, the same drawbacks are perceived to affect any quantitative assay that involve tape stripped skin, including quantitating RNA levels, as recited in the pending claims.

Finally, claims 71-72 recite that adhesive tape is applied to the skin between one and two times (claim 71) or one time (claim 72) to obtain the skin sample. Garofano et al. teach that tape is repeatedly applied "until the adhesive power is lost." The Office Action impliedly acknowledges that this requires more than 2 tape strippings by separating this rejection from the 35 U.S. C. 102

rejection above. However, as discussed above, the Office Action asserts that there is motivation and a reasonable expectation of success with one or two tape stripping. To support this assertion the Office Action cites Garofano's conclusion that the material stuck on adhesive tape can be considered an interesting source of DNA for investigation purpose. Furthermore, the Office Action cites Garofano's comments regarding performing genetic analysis using adhesive tapes that had been used to wrap packages in crime cases and in kidnapping cases, as evidence that Garofano et al. expected success even where only one tape stripping was used.

Applicants respectfully assert that it cannot be concluded that based on Garofano et al. one of ordinary skill in the art would reasonably expect success in isolating and quantitating RNA from a skin sample obtained by applying an adhesive tape to the skin one or two times. Garofano et al. repeatedly apply an adhesive to the skin until the adhesive power is lost. If Garofano et al. expected one or two tape strippings to be enough, they would have tape stripped only once or twice, not until the adhesive power was lost. Furthermore, the Office Action's conclusion that tape stripping in kidnapping cases and to wrap packages related to crimes, involves only one tape stripping is mere speculation. For example, in placing tape on a package, it is common to apply fingers to the tape numerous times while positioning the tape over the package. Therefore, Applicants respectfully assert that the Office Action's conclusion based on Garofano et al. that one of ordinary skill in the art would expect success in isolating a nucleic acid sample using only 1 or 2 tape strippings, is mere speculation. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 71-72 under 35 U.S.C. § 103(a) over Garofano et al. *Adv. Forensic Haemogentet.* 6:281-83 (1996).

Claims 77-78, 80-83, 149-154, 156-159, and 163-164 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al., in view of Paludan et al., *J. Invest. Derm.* 99:830-835 (1992). Applicants respectfully traverse the rejection. The Office Action cites its reasons of record in the prior Office Action, which cited Garofano et al. for teaching using tape stripping to detect DNA in skin samples, but acknowledges that Garofano et al. do not teach detection of RNA. However, the prior Office Action alleged that the teaching of Paludan et al. that IL-8 mRNA can be



assayed in samples obtained by skin scraping, makes it obvious to use the tape stripping method of Garofano et al. to detect mRNA of cytokines. The Office Action asserts that a skilled artisan would have expected success because Garofano et al. disclose that nucleated cells were obtained, which allegedly would be expected to contain RNA, as detected by Paludan et al.

Regarding the Applicants argument that the combination of Garofano et al. and Paludan et al. do not enable the present invention because they teach a low percentage of positive cells, the Office Action asserts that perfection is not required, merely the ability to detect the desired amino acid with a reasonable expectation of success. Furthermore, the Office Action asserts that Applicants have failed to make the case that one of ordinary skill in the art would not have been motivated to modify Garofano's method to include analysis of RNA as taught by Paludan et al. Finally, the Office Action asserts that Applicants' arguments regarding the lack of published reports are not persuasive, because allegedly one cannot conjecture as to why other groups have not pursued this line of experimentation.

Claims 77, 149-154, 156, and 163 are canceled herein, without prejudice or disclaimer. Therefore, the rejection of these claims is moot. Claim 64, from which claims 78, 80-83, 157-159 and 164 depend, recites that RNA is isolated from a skin sample obtained by applying an adhesive tape to the skin, and that levels of RNA in a skin sample are compared to a control sample, thereby quantitating relative expression of the RNA. Applicants respectfully assert that Garofano et al. in view of Paludan et al., do not provide a reasonable expectation of success regarding these claim limitations. Garofano et al. is silent with respect to isolating RNA and silent with respect to quantitating relative expression of any nucleic acid, including RNA. Furthermore, since Garofano et al. is silent with respect to quantitation of any nucleic acid and silent with respect to RNA isolation, there is no inherent teaching in Garofano et al. that RNA is isolated and quantitated. Although Paludan et al. teach quantitative analysis of RNA in skin samples, since Paludan et al. obtain their skin sample by scraping skin using a sterile blade until the skin is moist (Paludan et al., pg. 831, first paragraph of Results), the results of Paludan et al. do not provide the reasonable expectation of

success missing from the teaching of Garofano et al. with respect to isolation and quantitation of RNA in skin samples obtained by applying an adhesive strip to skin. The distinction between obtaining a sample by applying an adhesive tape to the skin, which leaves the skin virtually unblemished, versus scraping with a blade until the scraped area appears moist is significant because cells of the upper layers, but not deeper layers such as those obtained by scraping with a blade until the area is moist, do not actively transcribe RNA into protein.

Further evidence that Garofano et al. in view of Paludan et al. do not provide a reasonable expectation of success for the claimed invention is provided by the inconsistent results of Garofano et al. with respect to isolating DNA in skin samples obtained by applying an adhesive tape to the skin combined with the fact that Paludan et al. did not isolate the same cells that are isolated by applying an adhesive tape to the skin. Even for isolating DNA by applying an adhesive to the skin until the adhesive was gone, Garofano et al. report a relatively "low percentage of positive results" in samples obtained by applying adhesive tape to the skin (page 282, last paragraph). As acknowledged in the Office Action, "*all* work involving RNA is difficult, because *all* tissues and cells are rich in RNAases" (Office Action page 3, first full paragraph). However, the Office Action alleges that "there is no reason for the person of ordinary skill in the art to have expected skin cells obtained by tape stripping to be inordinately different in this respect." Applicants respectfully assert that a skilled artisan would not expect cells of the outer layers of the skin that are harvested by tape stripping to include intact RNA, especially not enough intact RNA to allow quantitation. Unlike almost all cells of the body, cells of the outer layers of the skin are devoid of organelles and do not actively transcribe RNA into protein. Therefore, one of ordinary skill in the art would not expect success in isolating and quantitating RNA from skin samples obtained by applying an adhesive tape to the skin, by Garofano et al.'s disclosure of the isolation of DNA from some skin samples, nor by Paludan et al.'s disclosure of nucleic acid analysis by scraping skin with a blade until the skin looked moist.

The teachings of Paludan et al. do not provide the missing expectation of success of Garofano et al. because Paludan et al. scraped skin using a blade until the area looked moist (Paludan et al., 831, first column of Results). Paludan et al. is silent with respect to applying an adhesive tape to the skin to obtain a skin sample. Therefore, the cells obtained in Paludan et al. are different than those obtained in the method of Garofano et al. Accordingly, the teaching of Paludan et al. regarding isolating and quantitating RNA cannot provide the reasonable expectation of success that is missing in Garofano et al. for isolating and quantitating RNA in skin samples obtained by applying an adhesive tape to the skin.

The fact that one of ordinary skill in the art would not have a reasonable expectation of success nor a motivation to use tape stripping to isolate and quantitate an RNA from the skin, is evidenced by the comments of NIH reviewers (EXHIBIT A) of a grant proposal that relies on methods of the present application, entitled "Non-Invasive Recovery of RNA from Human Epidermis," submitted by Dermtech International, the assignee of the present patent application, after the filing date of the present application. For example, Reviewer 1 asserted that "Existence of intact cellular mRNA in the outermost layer of St. corneum is surprising" (Exhibit A, page 2, paragraph entitled "APPROACH"). Furthermore, Reviewer 2 asserted that "[t]here was some concern about the over-all view of the investigators about skin biology and their hope that mRNA detection on the very superficial samples obtained from tape stripping would reflect salient mRNAs and DNA products that reflect what is going on [sic] in lower layers of the epidermis and the dermis" (Exhibit A, page 3, last paragraph.). Accordingly, Applicants assert that, as supported by Exhibit A, there is no motivation or reasonable expectation of success for the claimed methods, based on the teachings of Garofano et al.

The patentability of the present invention over the cited art is further established by a number of secondary factors, including long-felt need, unexpected results, commercial success and skepticism of experts. For example, experts were skeptical and the results unexpected regarding the ability to isolate and quantitate RNA from the outermost layer of stratum corneum using tape

stripping (See Exhibit A, Reviewer 1 comments on page 2, paragraph labeled “APPROACH,” asserting that “Existence of intact cellular mRNA in the outermost layer of St. corneum is surprising”; and Reviewer 2 comments on page 3, last paragraph “[t]here was some concern about the over-all [sic] view of the investigators about skin biology and their hope that mRNA detection on the very superficial samples obtained from tape stripping would reflect salient mRNAs and DNA products that reflect what is going on [sic] in lower layers of the epidermis and the dermis”). Regarding long-felt need, it is recognized that there is an important need for a non-invasive method for performing RNA analysis of the stratum corneum (See Exhibit A, Reviewer 1 comment on page 2, paragraph labeled “CRITIQUE 1, “This is an excellent proposal to test an innovative idea that could fill an important commercial and scientific need”). Furthermore, it is acknowledged that RNA analysis of the skin using a non-invasive, rapid method is expected to find wide application and commercial success (Exhibit A, Reviewer 1 comments on page 2, paragraph labeled “SIGNIFICANCE”; Reviewer 2 comments on page 3, paragraph labeled “SIGNIFICANCE,” “The idea of this grant proposal is novel and very advanced. This work would be the beginning of real molecular diagnoses in dermatology. It has the potential of making the overall entire field and discipline of dermatology revolutionized towards a more objective science for making the diagnoses and modulating therapy according to gene expression”).

Further evidence regarding a lack of expectation of success and skepticism of experts regarding the invention of the pending claims is exemplified by publications that assert that it is not possible to reliably quantitate a molecule in the outermost layers of skin using tape stripping. Tape harvesting or stripping of the stratum corneum has been used in dermatology for over 40 years to remove the outer layer of the epidermis to test for drug penetration pharmacokinetics. However, efforts to quantify the uptake of applied chemicals by assaying their content in the removed stratum corneum have encountered difficulty and skepticism (Bunge, A. and R. Guy (2003), “Improvement of methodology for assessing bioequivalence of topical products”

[http://www.fda.gov/ohrms/dockets/ac/03/slides/3996S2\\_07\\_Bunge.pdf](http://www.fda.gov/ohrms/dockets/ac/03/slides/3996S2_07_Bunge.pdf) (EXHIBIT B); and PRMA

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(1998), "Draft Guidance for Industry on Topical Dermatological Drug Product NDA's and ANDA's - In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies: Dermatopharmacokinetics (DPK) Method Issues:"

<http://srpub.phrma.org/letters/08.17.98.topical.derm.html> (EXHIBIT C)). This has lead to a withdrawal in 2003 of the FDA's guidance on using tape stripping for pharmacokinetic studies. This general opinion that tape stripping is not a sufficiently quantitative tool is powerfully evidenced by the opinion of the American Academy of Dermatology. In December of 1999 the Academy stated its opposition to the method (AAD, 1999) and suggested that that tape stripping was fundamentally doomed to failure (AAD (1999), Washington Report: Skin tape stripping method for generic dermatologic drug approval remains in question

[http://www.aadassociation.org/old/washReports/dec99\\_washrep.html](http://www.aadassociation.org/old/washReports/dec99_washrep.html) (EXHIBIT D)). Thus, it is evident that the practice of tape stripping was and is not viewed as a potentially quantitative method by two of the most influential associations in dermatological and pharmaceutical science. While these opinions are directed at the use of tape stripping for the dermatopharmacokinetic determination of bioequivalence, the same drawbacks are perceived to affect any quantitative assay that involve tape stripped skin, including quantitating RNA levels, as recited in the pending claims. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 77-78, 80-83, 149-154, 156-159, and 163-164 under 35 U.S.C. §103(a) as being unpatentable over Garofano et al., in view of Paludan et al., *J. Invest. Derm.* 99:830-835 (1992).

Claim 155 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al., for reasons of record. Claim 155 is canceled herein, without prejudice or disclaimer. Therefore, the rejection of this claim is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 155 under 35 U.S.C. §103(a) as being unpatentable over Garofano et al.

Claim 87 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Garofano et al., for reasons of record. Claim 87 is canceled herein, without prejudice or disclaimer. Therefore, the

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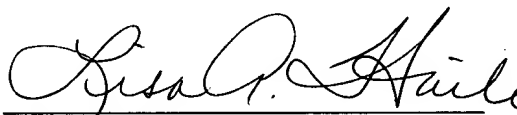
rejection of this claim is moot. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 87 under 35 U.S.C. §103(a) as being unpatentable over Garofano et al.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. Although no fee other than that submitted herewith is deemed necessary in connection with the filing of this Response, if any additional fee is required, the Commissioner is authorized to charge any fee (or credit any overpayment) to Deposit Acct. No. 50-1355.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Dated: April 23, 2004



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Enclosures: Exhibits A-D